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Translation

PATENT COOPERATION TREATY

PCT/FR2003/003458

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference FLAMEL0079QT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/FR2003/003458	International filing date (*day/month/year*) 24 novembre 2003 (24.11.2003)	Priority date (*day/month/year*) 04 décembre 2002 (04.12.2002)
International Patent Classification (IPC) or national classification and IPC C08G 69/10, 69/48, A61K 47/48, 9/50		
Applicant FLAMEL TECHNOLOGIES		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 03 juin 2004 (03.06.2004)	Date of completion of this report 22 October 2004 (22.10.2004)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FR2003/003458

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☒ the description:

pages 1-16, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the claims:

pages 1-21, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the drawings:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FR 03/03458

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-21	YES
	Claims		NO
Inventive step (IS)	Claims	1-21	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-21	YES
	Claims		NO

2. Citations and explanations

Reference is made to the following documents:

D1: HEESWIJK VAN W A R ET AL: "THE SYNTHESIS AND CHARACTERIZATION OF POLYPEPTIDE-ADRIAMYCIN CONJUGATES AND ITS COMPLEXES WITH ADRIAMYCIN. PART I" JOURNAL OF CONTROLLED RELEASE, ELSEVIER SCIENCE PUBLISHERS B. V. AMSTERDAM ,NL, vol. 1, 1985, pages 301-315, XP002059418, ISSN: 0168-3659 (cited in the application);

D2: EP-A-0 734 720 (FLAMEL TECH SA) 2 October 1996 (1996-10-02).

Document D1, which is considered to be the closest prior art, describes a polyglutamate grafted with an oligoamino acid, for example, Gly-Leu or Gly-Gly-Leu (see page 305, table 2; figure 3; page 312, column 1, paragraph 1), which polyglutamate is covalently bound to an active principle and is used as a biodegradable carrier (see page 302, column 1, paragraph 2; page 305, column 2; and page 306, column 1, paragraph 2). Said substance is non-toxic (see page 302, column 2, paragraph 2) and is stable at physiological pH (see page 309, column 1, paragraph 1).

It follows that the subject matter of claim 1 differs from D1 in that the amino acid units in said oligoamino acid are selected from those having an alkyl or an aryl grouping in alpha.

As a result, the subject matter of claim 1 is considered to be novel (PCT Article 33(2)).

According to the applicant, the inventive polyamino acid is advantageous in that it is capable of forming a stable colloidal aqueous suspension. Furthermore, the applicant has demonstrated that the polyamino acid of the invention can be combined with insulin, unlike non-grafted polyglutamate.

The problem solved by the present invention can therefore be considered to be that of designing an oligoamino acid-grafted polyglutamate that is capable of forming a stable colloidal aqueous suspension and can be favourably combined with active principles.

D2 describes block or random copolyamino acids of glutamate and leucine (see page 11, examples 3 and 4, table 1). The polyamino acids described can be used as carriers for active principles (see page 4, line 19 to line 22). They are non-toxic and stable at any pH between 4 and 13 (see page 4, line 37 to line 48). The polyamino acids described in D2 are particularly characterised in that they form colloidal suspensions that are stable over a broad pH range compatible with the pH of physiological media. D2 does not, however, mention that it is possible to graft the polyglutamates.

A person skilled in the art could infer from D2 that it

would be advantageous to modify the materials in D1 by replacing the glycine units with leucine so as to enhance the capacity of said material to form a colloidal suspension, which is stable over a broad pH range compatible with the pH of physiological media. However, since neither D1 nor D2 mentions the capacity of oligoamino acid-grafted polyamino acids to combine with active principles (because, in D1, the active principle is bound covalently, while D2 does not relate to grafted polyamino acids), it would not be obvious for a person skilled in the art to replace the glycine in the grafts of D1 with leucine.

As a result, the subject matter of claim 1 is considered to involve an inventive step (PCT Article 33(3)).

Claims 2-12 are dependent on claim 1. Claims 13-20 relate to a composition containing a polyamino acid defined by means of the same features as the polyamino acids in claim 1. The subject matter of claim 21 is a preparation method for a composition as per any one of claims 11, 12 or 13. It follows that, as such, these claims also fulfil the PCT requirements of novelty and inventive step.